fears. Science and industry alike are looking to the IARC study to provide a firm foundation for either assuaging public fears or enacting measures to protect against whatever health risks may come to light.

Lowering Water's Octane

Liquid carbon dioxide (CO_2) is a powerful solvent used for purposes such as extracting the peanut flavor from peanuts and decaffeinating coffee. Now, two scientist–entrepreneurs in Berkeley, California, say that it may also be the best way to remove the possibly carcinogenic fuel additive methyl tertiary butyl ether (MTBE) from groundwater.

Marc Sims, a chemical engineer, and his partner Jim Robinson, a molecular biologist, developed a device called PoroCrit that uses thin, microporous polypropylene tubes to expose the polluted liquid to pressurized liquid CO_2. Originally, the device was designed to extract food flavorings. Then, says Sims, "We realized just how similar MTBE is to all the flavor compounds that we were extracting."

PoroCrit works well on MTBE, says Sims, because the pollutant is about 100 times more soluble in CO_2 than it is in water. The membranous tubes in the device create over 50 m^2 of surface area through which the MTBE is drawn off through the micropores by the CO_2. The end result is cleaner, slightly carbonated water. Other water pollutants such as gasoline, benzene, and chlorinated solvents, which are also highly soluble in carbon dioxide, may also be removed from water by the device.

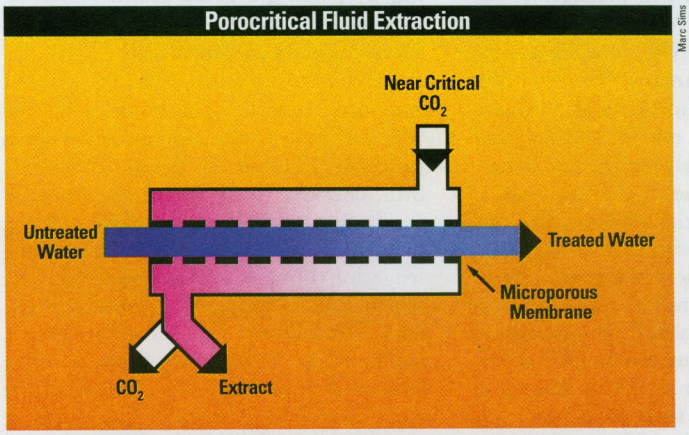
Originally introduced in 1979 as a way to boost the octane in gasoline, MTBE came into widespread use as a fuel additive because of its apparent ability to protect the public health by reducing automobile carbon monoxide emissions. In 1990, the Clean Air Act was amended to require the use of cleaner-burning fuels in areas with high carbon monoxide levels (those in nonattainment for National Ambient Air Quality Standards) in winter months. Oxygenated gasoline programs, including the use of MTBE, became the most popular means of meeting the new requirement. MTBE is currently found in about 25% of the gasoline used in the United States.

In 1996, however, it was discovered that the additive had found its way into the groundwater in Santa Monica, California, prompting the city to shut down half its water supply wells. Other studies found traces of MTBE in 5% of the wells across the United States. Scientists suspect that in most cases the chemical is released into the environment by leaking fuel storage tanks and is washed into wells by rainwater, which readily dissolves the chemical.

In December 1997, the EPA issued a health advisory alerting people to the possible danger of MTBE in water. The health effects of ingesting MTBE in the concentrations being found in drinking water are not known, but at high concentrations the chemical has been shown to cause cancer in animals. Even if the chemical does not pose a serious health risk, its strong taste and smell can seriously deteriorate the quality of the water in which it is found.

Once MTBE gets into water, it becomes very difficult to remove. MTBE is extremely soluble in water—about 30 times more soluble than benzene—and very resistant to biodegradation. Because it does not readily adsorb to soil particles (unlike other fuel constituents), it tends to travel with groundwater plumes, as fast as the water travels.

These characteristics of MTBE seriously hamper the effectiveness of traditional groundwater remediation techniques on the pollutant. Granular activated carbon filters, for example, do not work at all. Up until now, the best remediation technology for MTBE in water has been air stripping, an aeration technique in which MTBE concentrations of 20 parts per million (ppm) can be reduced to 10 ppm for about $16 per 1,000 gallons of water, including treatment of offgases. But Sims says his device can achieve much greater reductions in MTBE for around $5 per 1,000 gallons. And, he says, "It can be water that is saturated with MTBE, which is at [concentrations of] about 4%."



Anti-MTBE membrane. A new process that uses a microporous membrane shows promise for removing MTBE from drinking water.

The biggest challenge facing the researchers right now is scaling the device up from something that was used to extract flavors to something that can handle huge plumes of polluted groundwater. The device they've developed will be most effective where the volume of polluted groundwater is low and the MTBE concentration is high. They are testing a pilot version that can handle a few liters of water per minute. "What we want is a device that can handle about 20 gallons of water per minute, and that is portable so that you can put it on the back of a truck and take it to the site," Sims says. "If you [treat] the contaminant upstream, you don't have to deal with as many gallons. What we want to do is treat water at the source."

New System for Seafood Safety

In April, the U.S. General Accounting Office (GAO) released a disturbing report entitled *Food Safety: Federal Efforts to Ensure the Safety of Imported Foods Are Inconsistent and Unreliable.* The GAO report charges that the Food and Drug Administration (FDA) inspects less than 2% of all food imports, including seafood imports, adding fuel to public concerns about food safety. Imports now account for more than 55% of total U.S. seafood consumption, according to U.S. Department of Agriculture statistics.

The criticism came several months into the FDA's switch to a new program for seafood safety, known as the Hazard Analysis and Critical Control Point (HACCP, pronounced "hassip") system. First developed in the early 1960s to ensure good quality food for U.S. astronauts, HACCP was put forward by the FDA in 1995 as a process for ensuring better food quality for all consumers. The program became mandatory for the seafood industry in December 1997.

HACCP focuses on preventing hazards rather than relying on spot-checks and random sampling of products to catch them later. Under the new system, each food processor and importer prepares a plan for identifying the points in their operations most vulnerable to health hazards, depending on the product. The plan also describes the plant's procedures for preventing problems at each control point—that is, each point at which a potential hazard can be averted (for example, refrigeration)—and for monitoring them.

"On a pound-for-pound basis, seafood

is as safe as, if not more safe than, other meat sources," says Phillip Spiller, director of the FDA's Office of Seafood, in the November–December 1997 issue of *FDA Consumer*. Still, incidents of poisoning still occur and attract public attention. In early 1997, television news reports showed ambulances bearing away World Bank employees who fell ill from scombroid poisoning caused by blue marlin served in the Washington, DC, bank cafeteria. Twenty-six employees were affected.

The rising tide of seafood imports comes mainly from Canada, Asia, and Latin America. For shrimp, the most popular seafood product (shrimp cocktail remains the favorite appetizer among U.S. diners), Thailand and Ecuador are two of the main suppliers: of the 292 million kg of shrimp imported in 1997, 73.4 million kg came from Thailand and 63.7 million kg from Ecuador, according to U.S. Customs Service data. Mahi-mahi, another popular fish, comes mainly from Argentina, Taiwan, and Ecuador. For delicate foods traveling such great distances, refrigeration is the most critical control point. "A lot of it is time–temperature monitoring," says LeeAnn Applewhite, national sales manager of Seafood Diagnostics at Neogen Corporation, a private company that offers test kits and testing expertise to the food industry. "It can be real simple."

The main health risks of seafood consumption come from contaminated raw molluscan seafood (such as oysters and clams), histamine poisoning (or scombroid poisoning), and ciguatoxin, a natural toxin found in a few reef species. These three sources account for more than 90% of the outbreaks of seafood-borne illnesses and 75% of individual cases, according to the Centers for Disease Control and Prevention. The summer of 1997 saw the largest outbreak of *Vibrio parahaemolyticus* infections from raw oysters ever reported in North America: 209 people fell ill and one died. But most of the tainted oysters were harvested from California, Oregon, and Washington. Molluscan poisoning is mainly a problem with domestic seafood; few molluscan seafoods are imported, according to Steven Otwell, a professor of food science and human nutrition at the University of Florida in Gainesville.

For imports, the biggest risks relate to histamines, mainly from tuna and mahi-mahi. Histamines cause scombroid poisoning, which usually involves a rash, headaches, and itchy skin, and sometimes nausea and diarrhea. Scombrotoxin is a natural toxin that is produced in some fish species as soon as they die. Scombroid poisoning is relatively rare; from 1968 to 1980, 103 incidents affecting 827 people were reported. In 1992, 74 people on the East Coast suffered scombroid poisoning after eating tuna shipped from Ecuador.

Safe to eat? A new federal system for seafood safety seeks to ensure that seafood imports are free of environmental toxins.

Ecuador has had the worst reputation for exporting contaminated fish. "They still suffer from it," says Otwell, "but they've really cleaned up their act." Robert Price, a professor of food science and technology at the University of California at Davis and manager of the Seafood Network Information Center (NIC), says histamine-contaminated fish are often fish from Central America caught on long-lines and improperly refrigerated at sea.

Vibrio species of bacterial pathogens affect crabs and other shellfish. *V. vulnificus* can cause blood poisoning or gastroenteritis. For a particularly vulnerable group with an underlying illness such as cirrhosis or AIDS, it can cause primary septicemia—rare but lethal in 55% of cases. Ciguatera, a ciguatoxin, is produced mainly by tropical reef fish that are rarely eaten by the U.S. consumer, but may also appear in more commonly eaten fish such as mackerel and amberjack.

HACCP has had a swift impact on importers' procedures and their accountability. "HACCP has caused a lot of positive changes in our industry," says Applewhite. Most food science experts speak positively about HACCP and are helping the FDA raise awareness about its provisions. The Seafood HACCP Alliance, a consortium for training and education in the new system funded initially by the National Sea Grant College Program, is one of several organizations involved.

The alliance's goal is to provide a unified training program for the industry and regulators of the industry, according to Donn Ward, a professor of food science at North Carolina State University in Raleigh. Ward says that having importers and regulators receive training together encourages a common understanding of the rules. The training programs have drawn considerable interest from overseas suppliers and foreign governments. In September 1997, the alliance received Vice President Al Gore's National Performance Review Hammer Award, which recognizes partnerships that significantly improve the way federal agencies do their work.

The National Marine Fisheries Service, part of the National Oceanic and Atmospheric Administration (NOAA), conducts a voluntary HACCP training program that is broader in scope, emphasizing achieving quality over and above what is necessary for public health. Steven Wilson, chief quality officer for the NOAA Seafood Inspection Service, has seen overseas interest increase dramatically. "Five years ago [the amount of training provided] was zero," says Wilson. "Now it's one [training] a quarter." The Seafood NIC, in conjunction with the Alliance, bolsters such training by posting a great deal of HACCP information on its Web site at http://www-seafood.ucdavis.edu/home.htm.

The FDA will continue to conduct spot-checks, with 2,500 inspections and 9,432 laboratory tests of imported seafood products planned for Fiscal Year 1998. Still, checking every importer's HACCP verification procedures, in addition to the burden of inspection, poses a huge challenge for the agency. And inspections are not foolproof. The GAO report cites problems found by the U.S. Customs Service, which alleges that one seafood importer "removed a portion of the shipment that had thawed during transport before making the shipment available for FDA's inspection." The tampering led the FDA to

approve a shipment that it otherwise would have refused, according to the GAO report.

Critics hold that HACCP is no solution to the problem of food safety. "The results of HACCP to date in the seafood industry have been a disappointment, but not a surprise," says Caroline Smith DeWaal, director of food safety at the Center for Science in the Public Interest in Washington, DC. She claims that the task of checking for HACCP plans, to say nothing of shipment inspection, has overwhelmed the FDA. Smith DeWaal doesn't see much chance for improvement "without a lot of new resources going into the FDA's food safety program."

The FDA wants time for industry and regulators to adjust to the new system before making any assessment. "Any gauge [of HACCP] even prior to a year might be premature," says Ellen Nesheim, a consumer safety officer in the FDA's Office of Seafood in Washington, DC.

To help importers monitor shipments for HACCP compliance, several companies have developed rapid test kits. For example, Neogen offers a kit that tests histamine levels using an ELISA and yields visual color results in an hour. Third-party firms also offer help with HACCP monitoring, and importers hire them to train overseas suppliers. Neogen has seen its market soar and extend to countries such as Ecuador. "The onslaught has been tremendous," says Applewhite. "For HACCP, rapid methodology is about the only way to keep things online."

In public sector research, Rita Colwell, a professor at the University of Maryland's Center of Marine Biotechnology (COMB) in Baltimore, developed a kit for faster testing of *Vibrio cholerae*. COMB is also exploring biosensors for detecting polychlorinated biphenyls and heavy metals in seafood. Later in 1998, a portion of the FDA's marine toxins laboratories will be moved to COMB. "We're very excited about the FDA seafood people coming here," notes COMB director Yonathan Zohar. "Our expertise is complementary. It makes sense."

For both the seafood industry and the FDA, equivalency agreements that help ensure source countries' application of HACCP standards mark the next step. Without these bilateral agreements, importers must take measures themselves to ensure their suppliers' compliance. Faced with the daunting task of assessing foreign countries' food safety systems, however, the FDA has not moved quickly. "Many foreign governments have complained to us," according to Richard Gutting, Jr., senior executive vice president of the National

Tracking Toxicology

This year, the National Toxicology Program (NTP) celebrates 20 years of coordinating toxicology research and testing within the Department of Health and Human Services. The NTP is charged by Congress with providing federal regulatory and research agencies, as well as the general public, with information about chemicals that are potentially toxic to humans, and with strengthening the science base in toxicology. In carrying out its mission over the past two decades, the NTP has emerged as the leading force in designing, conducting, and extrapolating animal assays for toxicity and carcinogenicity. The NTP home page, located at http://ntp-server.niehs.nih.gov/, now offers access to much of the information gleaned by this program.

The About the NTP link on the home page leads to an overview of the program and a description of the evolving strategies being undertaken in order to more efficiently evaluate chemicals for toxic effects. This link also connects to the program's annual plan, which details upcoming and ongoing NTP projects within the three institutes that conduct the program's studies: the NIEHS, the National Institute for Occupational Safety and Health (a division of the Centers for Disease Control and Prevention), and the National Center for Toxicological Research (a division of the Food and Drug Administration).

The News, Events, & Special Reports link leads to a list of press releases, *Federal Register* announcements, and other items of interest. Visitors can also browse the *Liaison Office Update*, a regularly published collection of news items from the NTP Liaison and Scientific Review Office. The News link allows users to review NTP documents that are open for public comment, as well as submit feedback online.

The NTP Studies & Study Results link accesses the heart of the NTP—the actual studies and their results. From this page, users can search a database of completed NTP studies on individual chemical agents and view either the abstract, the chemical health and safety information sheet, or graphic illustrations for a particular study. Users can also view status reports for ongoing studies, as well as specially distilled report data culled from NTP studies, such as an index of specific tumor sites and the carcinogens associated with each site.

The Nomination & Selection Process link leads to information about the process for nominating chemicals to be reviewed by the NTP, and allows users to make nominations. Nominations are welcomed from academia, federal and state regulatory and health agencies, industry, environmental groups, and the general public. The NTP uses such nominations to help prioritize the chemicals to be studied in each fiscal year.

The NTP home page offers access to the current published version of the *Report on Carcinogens*, which lists chemicals as "known human carcinogens" or "reasonably anticipated to be human carcinogens," through the Environmental Health Information Service (located at http://ehis.niehs.nih.gov). Viewers can also check on the status of the next version of the report. This link also describes the procedures and criteria for nominating substances for listing or delisting in the report, and contains information on what chemicals are currently under review for future inclusion in the report.

Access to the home pages for the NTP Center for Evaluation of Alternative Toxicological Methods and the NTP Center for Evaluation of Risks to Human Reproduction is available from the NTP site. Each of these centers has its own unique mission. The human reproduction center will assess the human reproductive risks from chemicals and chemical mixtures, and provide a centralized source of public information on such risks, while the alternative methods center will attempt to identify more efficacious means for identifying the toxic effects of chemicals.

The Request Information, Receive Announcements, and Publications links allows visitors to subscribe to the NTP List Server to receive program news and updates via e-mail, as well order some NTP publications.

Fisheries Institute, an industry association located in Arlington, Virginia. "They've submitted their requests, but the FDA is slow to move."

Still, says Otwell, "My bottom line is that seafood remains the safest source of muscle protein in the world." And contrary to the current situation, which focuses on concerns about safety, Otwell maintains that in the next 20 years "the biggest [issue] will be availability, period."

One-upping the LD50

Since the 1920s, the most common method for testing a chemical for its acute oral toxicity after a single exposure has been to "feed" it (by oral gavage) in different amounts to groups of rats and then do a body count. This test is called the LD50, for lethal dose 50%—the dose at which half of the rats died. Measured in milligrams per kilogram (mg/kg) body weight, the LD50 helps classify and label chemical hazards in the workplace, at home, and in cases of accidental release.

But the LD50, the so-called classical method, has come under sharp criticism from animal welfare advocates for its use of 30–100 rats per test. In response, researchers at the Food and Drug Administration (FDA), the EPA, and Procter & Gamble have developed a new alternative test method that was approved by the Organisation for Economic Co-operation and Development (OECD) in June for use by its member countries. The new method is called the "up-and-down" procedure and uses a fraction of the number of laboratory animals used in the LD50 while producing enough information to evaluate the consequences of single chemical exposures and to serve as a basis for hazard classification and labeling.

"The up-and-down procedure reduces the number of animals used by two-thirds," says Katherine Stitzel, associate director of the human and environmental safety division at Procter & Gamble. "The classical method typically uses 30 animals; this alternative method uses 6–10. In the classical method, you dose all the animals at the same time, so you might kill all the animals at the same time as well. But by dosing them one at a time with the up-and-down, you don't have a lot of deaths."

While still using the term "LD50" as a unit of measure, the alternative method was designed to reduce the pain and suffering of laboratory animals. One rat is weighed and tested per day, followed by a wait of 24 hours to observe the outcome. The dose is then raised or lowered for each subsequent animal, depending on the outcome of the previous test. For example, if the first rat survives the dose, the second is given a higher amount. Conversely, if the first rat dies, the next receives a lower dose. The higher and lower dose changes are adjusted by a constant multiplicative factor, usually 1.3. The process is repeated until 4 animals have been dosed after reversal of the initial outcome.

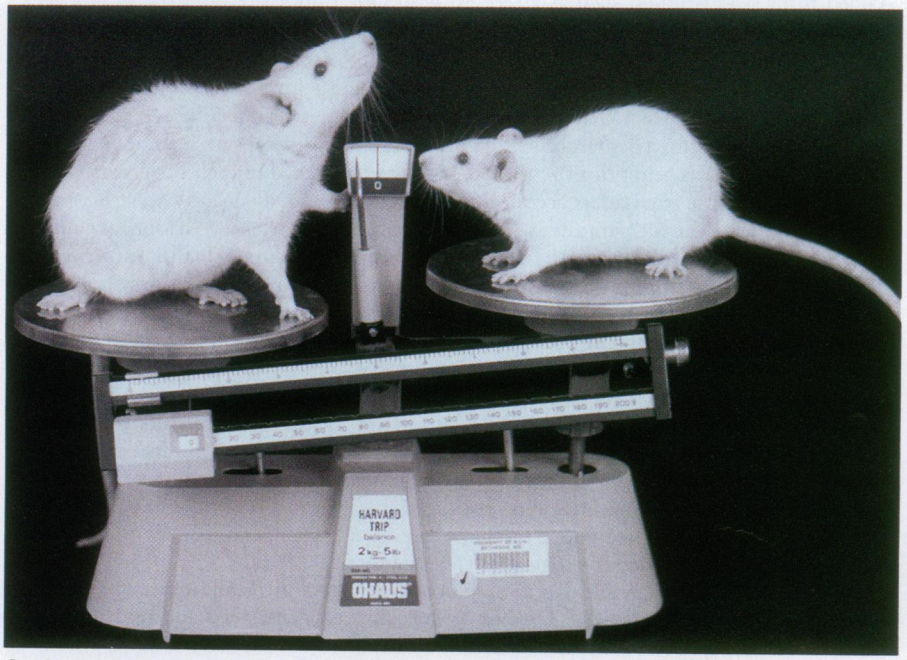
The LD50 for each chemical can then be calculated. The lower the LD50, the less of a certain chemical is required to kill an animal. For example, the LD50 of table salt is 3,300 mg/kg; for acephate (an insecticide), the LD50 is 1,494 mg/kg. For chemicals classified as poisons, the LD50 can be as low as 4 mg/kg (for the pesticide parathion). The LD50s of different substances are printed on the labels of insecticides, pesticides, and other chemicals, accompanied by the words "danger," "poison," "warning," or "caution."

"I see a benefit [of the new method] in terms of fewer animals dying and suffering in comparison to the classical method," says Andrew Rowan, senior vice president for research, education, and international issues at The Humane Society of the United States. The animals are also observed for signs of severe distress, pain, or impending death so that they may be humanely euthanized. "Some still suffer with the up-and-down," says Rowan, "but each is given more attention. When symptoms are observed, something can be done. The classical test method was badly in need of replacement by something like the up-and-down."

"Another advantage to the up-and-down procedure is that it provides a more accurate estimate of the LD50 than other OECD test methods," says William Stokes, alternative models group leader of the Environmental Toxicology Program at the NIEHS. "Other methods only give a range for the LD50, and for classification and labeling, this range is generally adequate. But the more accurate estimate with the up-and-down method helps set the dose for subsequent studies and helps when mixing that chemical with other substances. For chemicals that will be used in mixtures, this more accurate estimate will reduce the need for additional LD50 testing."

This more accurate estimate, adds Stitzel, "is a great advantage to us when we market around the world. With the classical method, you test at levels that fit a classification system. But in the United States, we don't use the same classification system as they use in Europe. The up-and-down method comes up with a number [for the LD50] using a statistical method. And it's statistics that allow you to do them one at a time. The number is what's most important."

The up-and-down procedure should mean greater efficiency in laboratories and better conditions for test animals. According to Stitzel, the OECD is currently debating whether to drop the classical method from its guidelines.



Good news for rats and researchers. Approval of the so-called up-and-down procedure means testing for chemical hazards will involve fewer rats and provide researchers with more accurate information.